Genome-wide association study identifies 30 loci associated with bipolar disorder

eQTLGen Consortium; BIOS Consortium; the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium

published in
Nature Genetics
2019

DOI (link to publisher)
10.1038/s41588-019-0397-8

document version
Publisher's PDF, also known as Version of record

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-019-0397-8

Genome-wide association study identifies 30 loci associated with bipolar disorder

Bipolar disorder is a highly heritable psychiatric disorder. We performed a genome-wide association study (GWAS) including 20,352 cases and 31,358 controls of European descent, with follow-up analysis of 822 variants with $P < 1 \times 10^{-4}$ in an additional 9,412 cases and 137,760 controls. Eight of the 19 variants that were genome-wide significant ($P < 5 \times 10^{-8}$) in the discovery GWAS were not genome-wide significant in the combined analysis, consistent with small effect sizes and limited power but also with genetic heterogeneity. In the combined analysis, 30 loci were genome-wide significant, including 20 newly identified loci. The significant loci contain genes encoding ion channels, neurotransmitter transporters and synaptic components. Pathway analysis revealed nine significantly enriched gene sets, including regulation of insulin secretion and endocannabinoid signaling. Bipolar I disorder is strongly genetically correlated with schizophrenia, driven by psychosis, whereas bipolar II disorder is more strongly correlated with major depressive disorder. These findings address key clinical questions and provide potential biological mechanisms for bipolar disorder.

Bipolar disorder (BD) is a severe neuropsychiatric disorder characterized by recurrent episodes of mania and depression that affect thought, perception, emotion and social behavior. A lifetime prevalence of 1–2%, elevated morbidity and mortality, onset in young adulthood and a frequently chronic course make BD a major public health problem and a leading cause of the global burden of disease[1]. Clinical, twin and molecular genetic data all strongly suggest that BD is a multifactorial disorder[2]. On the basis of twin studies, the overall heritability of BD has been estimated to be more than 70% (refs. [3,4]), suggesting a substantial involvement of genetic factors in the development of the disorder, although non-genetic factors also influence risk.

BD can be divided into two main clinical subtypes[5,6]: bipolar I disorder (BD1) and bipolar II disorder (BD2). In BD1, manic episodes typically alternate with depressive episodes during the course of illness. BD2 diagnosis is based on the lifetime occurrence of at least one depressive and one hypomanic (but not manic) episode. Although modern diagnostic systems retain the Kraepelinian dichotomy[7] between BD and schizophrenia (SCZ), the distinction between the two disorders is not always clear-cut and patients who display clinical features of both disorders may receive a diagnosis of schizoaffective disorder–bipolar type (SAB). Likewise, in genetic studies, BD and SCZ are usually treated separately, although recent epidemiological and molecular genetic studies provide strong evidence for some overlap between the genetic contributions to their etiology[2,8].

Recent genome-wide association studies in BD have identified a number of significant associations between disease status and common genetic variants[9–23]. The first large collaborative BD GWAS by the multinational Psychiatric Genomics Consortium (PGC) Bipolar Disorder Working Group comprised 7,481 patients with BD and 9,250 controls and identified four genome-wide-significant loci[9]. Three subsequent meta-analyses that included the PGC BD data[10,12,18] identified an additional four loci.

Estimates of the proportion of variance in liability attributable to common variants genome wide (SNP heritability) indicate that ~30% of the heritability for BD is due to common genetic variants[8]. So far, only a small fraction of this heritability is explained by associated loci, but results from other human complex traits suggest that many more will be identified by increasing the sample size of GWAS[24]. Here, we report the second GWAS of the PGC Bipolar Disorder Working Group, comprising 20,352 cases and 31,358 controls of European descent in a single, systematic analysis, with follow-up of top findings in an independent sample of 9,412 cases and 137,760 controls. Some of our findings reinforce specific hypotheses regarding BD neurobiology; however, the majority of the findings suggest new biological insights.

Results

GWAS of BD. We performed a GWAS meta-analysis of 32 cohorts from 14 countries in Europe, North America and Australia (Supplementary Table 1a), totaling 20,352 cases and 31,358 controls of European descent (effective sample size 46,582). This is a large GWAS of BD, a 2.7-fold increase in the number of cases compared with our previous GWAS[9] and includes 6,328 case and 7,963 control samples not previously reported. We imputed variant dosages using the 1000 Genomes reference panel, retaining association results for 9,372,253 autosomal variants with imputation quality score INFO > 0.3 and minor allele frequency (MAF) ≥1% in both cases and controls. We performed logistic regression of case status on imputed variant dosage using genetic ancestry covariates. The resulting genomic inflation factor (λ_{GC}) was 1.23, 1.01 when scaled to 1,000 cases and 1,000 controls ($\lambda_{1,000}$) (Supplementary Fig. 1). The linkage disequilibrium (LD) score regression intercept was 1.021 (s.e.m. = 0.010), and the attenuation ratio of 0.053 (s.e.m. = 0.027) was non-significant, indicating that the observed genomic inflation is indicative of polygenicity rather than stratification or cryptic population structure[25]. The LD score regression SNP heritability estimates for BD were 0.17–0.23 on the liability scale assuming population prevalence of 0.5–2% (see Supplementary Table 1a, Methods and Supplementary Note for sample and method details).

We found a marked increase in phenotypic variance explained by genome-wide polygenic risk scores (PRS) compared with previous publications (sample size weighted-mean-observed Nagelkerke's $R^2 = 0.08$ across datasets, liability scale $R^2 = 0.04$, for P threshold of 0.01; Supplementary Fig. 2 and Supplementary Table 2). Among the different datasets, we observed no association between the PRS R^2

A full list of authors and affiliations appears at the end of the paper.

and: (1) the sex distribution of the BD cases ($P=0.51$); (2) the proportion of cases with psychosis ($P=0.61$); (3) the proportion with a family history of BD ($P=0.82$); or (4) the median age of onset for BD ($P=0.64$). In our primary genome-wide analysis, we identified 19 loci exceeding genome-wide significance ($P<5\times10^{-8}$; Table 1).

Follow-up of suggestive loci in additional samples. We tested lead variants that were significant at $P<1\times10^{-4}$ in our discovery GWAS meta-analysis, comprising a total of 794 autosomal and 28 X-chromosome variants, for association in follow-up samples totaling 9,412 cases and 137,760 controls of European ancestry (effective sample size 23,005; Supplementary Note and Supplementary Table 1b). We first compared discovery and follow-up sample summary statistics using LD score regression, and estimated their genetic correlation to be 0.98 (s.e.m. = 0.07), consistent with homogeneous genetic effects between the two samples. Discovery and follow-up samples also show similar patterns of significant genetic correlations with a range of other human diseases and traits in the LD Hub database[26] (Supplementary Table 3; correlation of 0.93, $P=8.3\times10^{-14}$, Supplementary Fig. 3).

Thirty autosomal loci achieved genome-wide significance ($P<5\times10^{-8}$) in fixed-effect meta-analysis of our GWAS and follow-up samples (Fig. 1, Table 1a, Supplementary Data 1–3 and Supplementary Table 4). In Supplementary Table 5, we present detailed descriptions of the associated loci and genes, with bioinformatic and literature evidence for their potential roles in BD. Of the 30 genome-wide-significant loci from our combined analysis, 20 are novel BD risk loci. These include 19 loci that were significant only in the combined analysis, of which 3 were reported to have genome-wide-significant SNPs in previous studies (*ADCY2* (ref. [18]), *POU3F2* (ref. [18]), *ANK3* (refs. [12,18])), and 11 that were significant in our primary GWAS. We refer to loci by the gene name attributed in previous BD GWAS publications, or by the name of the closest gene for newly identified loci, without implication that the named gene is causal. Results for all variants tested in the follow-up study are presented in Supplementary Table 4.

Of the 19 variants that were genome-wide significant in the discovery GWAS, 8 were not genome-wide significant in the combined analysis (Table 1b), and 11 were non-significant in one-tailed association tests in the follow-up samples ($P>0.05$ in Table 1). Still, the follow-up results for these 19 variants are clearly non-null in aggregate: all 19 had consistent directions of effect between discovery GWAS and follow-up (9.5 expected by chance, binomial test $P=4\times10^{-6}$), and 8 of the 19 had follow-up one-tailed $P<0.05$ (1 expected by chance, sign test $P=2\times10^{-6}$). Using effect sizes corrected for winner's curse[27,28] for each of the 19 variants that were genome-wide significant in the GWAS, we calculated power to achieve significant results (one-tailed $P<0.05$) in the follow-up samples or genome-wide significance in combined analysis (Supplementary Note, Supplementary Table 6 and Supplementary Fig. 4). We found that the number of variants significant in follow-up was close to expectation (8 observed with follow-up $P<0.05$, 8.26 expected, Poisson binomial $P=0.57$), and that 11 variants achieving genome-wide significance in the combined analysis were also within the expected range ($P=0.29$). As an alternative to winner's curse correction, we conducted a polygenic inference analysis using a mixture of Gaussian effect size distributions to model BD genetic architecture and estimate the variants' true effect sizes[29] (Supplementary Note and Supplementary Fig. 5). Under this model, we found that only two variants were nominally significantly weaker in follow-up than expected by chance (*TRANK1*, rs9834970 $P=0.012$, and rs13821 $P=0.026$; Supplementary Table 7), and none were Bonferroni significant ($P>0.05/19=0.0026$). Thus, the overall replication rate is within the expected range given the polygenic architecture of BD.

We next asked if the variants tested in the follow-up samples were, in aggregate, consistent with the presence of additional sub genome-wide-significant BD association signals. After excluding 47 variants that were genome-wide significant in our GWAS, our combined analysis or previous BD GWAS, 775 variants remained in our follow-up experiment. Of these, 551 variants had the same direction of effect in the discovery GWAS and follow-up (71%, compared to a null expectation of 50%, sign test $P=1.3\times10^{-32}$), and 110 variants had the same direction of effect and were nominally significant ($P<0.05$) in the follow-up (14%, compared to an expected value of 5%, binomial test $P=2.1\times10^{-22}$). This consistency between our GWAS and follow-up results suggests that many more true BD associations exist among these variants.

To identify additional independent signals, we conducted conditional analyses across each of the 30 significant BD loci (Supplementary Table 8). We used the effective number of independent variants on the basis of LD structure within loci[30] to calculate a multiple test-corrected significance threshold ($P=1.01\times10^{-5}$, see Supplementary Note). Only one locus showed evidence for an independent association signal (rs114534140 in locus no. 8, *FSTL5*; $P_{conditional}=2\times10^{-6}$). At another locus (no. 30, *STK4* on chromosome 20), we found two SNPs with genome-wide significance in low LD ($r^2<0.1$); however, conditional analysis showed that their associations were not independent.

Shared loci and genetic correlations with other traits. We next examined the genetic relationships of BD to other psychiatric disorders and traits. Of the 30 genome-wide-significant BD loci, 8 also harbor schizophrenia (SCZ) associations[31,32]. On the basis of conditional analyses, the BD and SCZ associations appear to be independent at three of the eight shared loci (*NCAN*, *TRANK1* and chr7q22.3:105 megabases (Mb)) (Supplementary Table 9). No genome-wide-significant BD locus overlapped with those identified for depression (DEPR), including 44 risk loci identified in the most recent PGC GWAS of major depression[33] and those reported in a large study of depressive symptoms or subjective well-being[34]. As previously reported[35], we found substantial and highly significant genetic correlations between BD and SCZ[31] (LD score regression estimated genetic correlation $r_g=0.70$, s.e.m. = 0.020) and between BD and DEPR[33] ($r_g=0.35$, s.e.m. = 0.026). The BD and DEPR genetic correlation was similar to that observed for SCZ and DEPR ($r_g=0.34$, s.e.m. = 0.025) (Supplementary Table 10a).

We found significant genetic correlations between BD and other psychiatric-relevant traits (Supplementary Table 10b), including autism spectrum disorder[8] ($r_g=0.18$, $P=2\times10^{-4}$), anorexia nervosa[36] ($r_g=0.23$, $P=9\times10^{-8}$) and subjective well-being[34] ($r_g=-0.22$, $P=4\times10^{-7}$). There was suggestive positive overlap with anxiety disorders ($r_g=0.21$, $P=0.04$)[37] and neuroticism ($r_g=0.12$, $P=0.002$)[38]. Significant r_g values were seen with measures of education: college attendance[39] ($r_g=0.21$, $P=1=x10^{-7}$) and education years[40] ($r_g=0.20$, $P=6\times10^{-14}$), but not with childhood IQ[41] ($r_g=0.05$, $P=0.5$) or intelligence[42] ($r_g=-0.05$, $P=0.08$). Among a large number of variants in BD risk loci that were associated with additional traits in the GWAS catalog[43], we found a handful of loci with non-independent associations (in one overlapping locus with each of educational attainment, biliary atresia, bone mineral density and lipid-related biomarkers) (Supplementary Table 9). Biliary atresia and lipid-related biomarkers, however, did not show significant genetic correlation with BD (Supplementary Table 10b).

BD subtypes. We performed a secondary GWAS focusing on three clinically recognized subtypes of bipolar disorder: BD1 ($n=14,879$ cases), BD2 ($n=3,421$ cases) and SAB ($n=977$ cases) (Supplementary Note, Supplementary Tables 1a and 11 and Supplementary Fig. 6). We observed variants in 14 loci with genome-wide significance

Table 1 | Genome-wide-significant bipolar disorder risk loci

Locus name[a]	Lead SNP	Chr	Base pairs	A1/A2	GWAS meta-analysis			Follow-up samples		Combined	
					Freq. A1	OR	*P* value[b]	OR	*P* value[c]	OR	*P* value[b]
(a) 30 loci with lead SNP $P<5\times10^{-8}$ in combined GWAS + follow-up analysis											
1, *PLEKHO1*	rs7544145	1	150,138,699	T/C	0.81	1.095	4.8×10^{-7}	1.064	**0.010**	1.085	$\mathbf{4.8\times10^{-8}}$
2, *LMAN2L*[d]	rs57195239	2	97,376,407	I/D	0.34	0.92	$\mathbf{5.8\times10^{-9}}$	0.96	**0.030**	0.93	$\mathbf{3.8\times10^{-9}}$
3, *SCN2A*	rs17183814	2	166,152,389	A/G	0.075	0.87	1.5×10^{-7}	0.89	**0.0017**	0.88	$\mathbf{2.0\times10^{-9}}$
4, [Intergenic][e]	rs61332983	2	194,465,711	I/D	0.41	0.93	$\mathbf{2.3\times10^{-8}}$	0.95	**0.0031**	0.93	$\mathbf{7.9\times10^{-10}}$
5, *TRANK1*[d]	rs9834970	3	36,856,030	T/C	0.51	0.90	$\mathbf{5.5\times10^{-14}}$	0.98	0.15	0.93	$\mathbf{5.7\times10^{-12}}$
6, *ITIH1*[d]	rs2302417	3	52,814,256	A/T	0.49	0.92	$\mathbf{4.9\times10^{-9}}$	0.94	**0.0012**	0.93	$\mathbf{6.6\times10^{-11}}$
7, *CD47*	rs3804640	3	107,793,709	A/G	0.53	1.075	9.3×10^{-8}	1.044	**0.016**	1.065	$\mathbf{2.0\times10^{-8}}$
8, *FSTL5*	rs11724116	4	162,294,038	T/C	0.16	0.90	$\mathbf{3.3\times10^{-8}}$	0.95	**0.031**	0.92	$\mathbf{2.4\times10^{-8}}$
9, *ADCY2*[d]	rs200550695	5	7,587,236	I/D	0.82	0.91	1.2×10^{-7}	0.94	**0.011**	0.92	$\mathbf{1.5\times10^{-8}}$
10, *SSBP2*	rs10035291	5	80,796,368	T/C	0.68	1.081	1.1×10^{-7}	1.047	**0.018**	1.070	$\mathbf{2.7\times10^{-8}}$
11, *RIMS1*	rs57970360	6	72,519,394	D/I	0.44	1.066	3.1×10^{-6}	1.062	**0.0016**	1.064	$\mathbf{3.5\times10^{-8}}$
12, *POU3F2*[e]	rs2388334	6	98,591,622	A/G	0.52	0.93	8.6×10^{-8}	0.95	**0.0051**	0.94	$\mathbf{4.0\times10^{-9}}$
13, *RPS6KA2*	rs10455979	6	166,995,260	C/G	0.53	0.93	$\mathbf{4.6\times10^{-8}}$	0.97	**0.046**	0.94	$\mathbf{4.3\times10^{-8}}$
14, *THSD7A*	rs113779084	7	11,871,787	A/G	0.30	1.068	7.3×10^{-6}	1.095	$\mathbf{2.9\times10^{-5}}$	1.076	$\mathbf{2.5\times10^{-9}}$
15, *SRPK2*	rs73188321	7	105,048,158	T/C	0.33	0.92	7.0×10^{-8}	0.94	**0.0015**	0.92	$\mathbf{1.1\times10^{-9}}$
16, *MRPS33*	rs201231874	7	140,700,006	D/I	0.25	0.92	9.4×10^{-8}	0.93	**0.0008**	0.92	$\mathbf{6.2\times10^{-10}}$
17, *ANK3*[d]	rs10994318	10	62,125,856	C/G	0.057	1.151	4.5×10^{-7}	1.130	**0.0021**	1.145	$\mathbf{6.8\times10^{-9}}$
18, *ADD3*[d]	rs59134449	10	111,745,562	I/D	0.16	1.105	5.0×10^{-8}	1.059	**0.017**	1.090	$\mathbf{1.2\times10^{-8}}$
19, *FADS2*[d]	rs12226877	11	61,591,907	A/G	0.29	1.095	$\mathbf{1.2\times10^{-8}}$	1.062	**0.0073**	1.085	$\mathbf{9.9\times10^{-10}}$
20, *PACS1*	rs10896090	11	65,945,186	A/G	0.81	1.094	2.1×10^{-7}	1.062	**0.0089**	1.084	$\mathbf{1.9\times10^{-8}}$
21, *PC*	rs7122539	11	66,662,731	A/G	0.35	0.93	2.2×10^{-7}	0.96	**0.015**	0.94	$\mathbf{3.8\times10^{-8}}$
22, *SHANK2*	rs12575685	11	70,517,927	A/G	0.31	1.066	1.2×10^{-5}	1.088	$\mathbf{5.7\times10^{-5}}$	1.073	$\mathbf{7.7\times10^{-9}}$
23, *CACNA1C*[d]	rs10744560	12	2,387,099	T/C	0.34	1.087	$\mathbf{2.9\times10^{-9}}$	1.052	**0.0086**	1.076	$\mathbf{3.6\times10^{-10}}$
24, *STARD9*	rs4447398	15	42,904,904	A/C	0.12	1.112	1.1×10^{-7}	1.072	**0.0079**	1.099	$\mathbf{9.4\times10^{-9}}$
25, *ZNF592*	rs139221256	15	85,357,857	I/D	0.28	0.92	$\mathbf{8.5\times10^{-9}}$	0.97	0.082	0.93	$\mathbf{2.7\times10^{-8}}$
26, *GRIN2A*	rs11647445	16	9,926,966	T/G	0.65	0.93	1.2×10^{-7}	0.93	$\mathbf{9.8\times10^{-5}}$	0.93	$\mathbf{1.1\times10^{-10}}$
27, *HDAC5*	rs112114764	17	42,201,041	T/G	0.69	0.93	1.7×10^{-6}	0.94	**0.0021**	0.93	$\mathbf{2.5\times10^{-8}}$
28, *ZCCHC2*	rs11557713	18	60,243,876	A/G	0.29	1.074	1.2×10^{-6}	1.059	**0.0038**	1.069	$\mathbf{3.6\times10^{-8}}$
29, *NCAN*[d]	rs111444407	19	19,358,207	T/C	0.15	1.124	$\mathbf{2.4\times10^{-10}}$	1.040	0.075	1.097	$\mathbf{1.3\times10^{-9}}$
30, *STK4*	rs202012857	20	43,682,549	I/D	0.28	0.923	3.0×10^{-7}	0.942	**0.0043**	0.929	$\mathbf{1.1\times10^{-8}}$
(b) Additional loci with lead SNP $P<5\times10^{-8}$ in GWAS analysis											
TFAP2B	rs55648125	6	50,816,718	A/G	0.90	0.89	$\mathbf{4.9\times10^{-8}}$	0.95	0.068	0.91	8.5×10^{-8}
DFNA5	rs17150022	7	24,771,777	T/C	0.88	0.89	$\mathbf{2.7\times10^{-8}}$	0.96	0.087	0.91	8.6×10^{-8}
SLC25A17	rs138321	22	41,209,304	A/G	0.50	1.083	$\mathbf{4.7\times10^{-9}}$	1.012	0.28	1.060	1.9×10^{-7}
HLF	rs884301	17	53,367,464	T/C	0.37	1.084	$\mathbf{5.8\times10^{-9}}$	1.013	0.26	1.061	2.1×10^{-7}
PHF15	rs329319	5	133,906,609	A/G	0.43	1.082	$\mathbf{1.5\times10^{-8}}$	1.019	0.18	1.061	2.1×10^{-7}
ODZ4[d]	rs73496688	11	79,156,748	A/T	0.14	1.11	$\mathbf{1.0\times10^{-8}}$	1.016	0.29	1.083	4.2×10^{-7}
[Intergenic][e]	rs57681866	2	57,975,714	A/G	0.06	0.85	$\mathbf{5.0\times10^{-8}}$	0.97	0.23	0.89	1.2×10^{-6}
[Intergenic][e]	rs13231398	7	110,197,412	C/G	0.11	0.89	$\mathbf{3.4\times10^{-8}}$	0.998	0.47	0.92	4.6×10^{-6}

[a] Loci are numbered 1 to 30, ordered by genomic position, with previously reported gene name for published loci. [b] *P* values for GWAS and combined analyses are two-tailed and bold if $P<5\times10^{-8}$. [c] *P* values for follow-up are one-tailed on the basis of the direction of effect in the discovery GWAS and bold if $P<0.05$. [d] Previously published and named loci. (Locus 12 would be named as Intergenic; nearest gene is *POU3F2* 691 kb.) [e] Intergenic loci nearest genes: locus 4 *PCGEM1* 824 kb, (**b**) chr2 locus *VRK2* 298 kb, (**b**) chr7 *IMMP2L* 106 kb.

for BD1, 10 of which were in genome-wide-significant loci in the combined BD GWAS analysis. Not surprisingly, given the sample overlap, three of the four remaining loci genome-wide significant for BD1 have $P<10^{-6}$ in either our discovery GWAS or combined analysis. The remaining locus (*MAD1L1*, chr7:1.9 Mb, discovery GWAS $P=2.4\times10^{-6}$) was recently published in two BD GWAS that included Asian-ancestry samples[17,44]. We did not observe genome-wide-significant results for the smaller BD2 and SAB analyses. BD1, BD2 and SAB all have significant common variant heritabilities (BD1 $h^2_{snp}=0.25$, s.e.m. $=0.014$, $P=3.2\times10^{-77}$; BD2 $h^2_{snp}=0.11$, s.e.m. $=0.028$, $P=5.8\times10^{-5}$; SAB $h^2_{snp}=0.25$, s.e.m. $=0.10$, $P=0.0071$). Genetic correlations among BD subtypes show that these represent closely related, yet partially distinct, phenotypes (Supplementary Table 12).

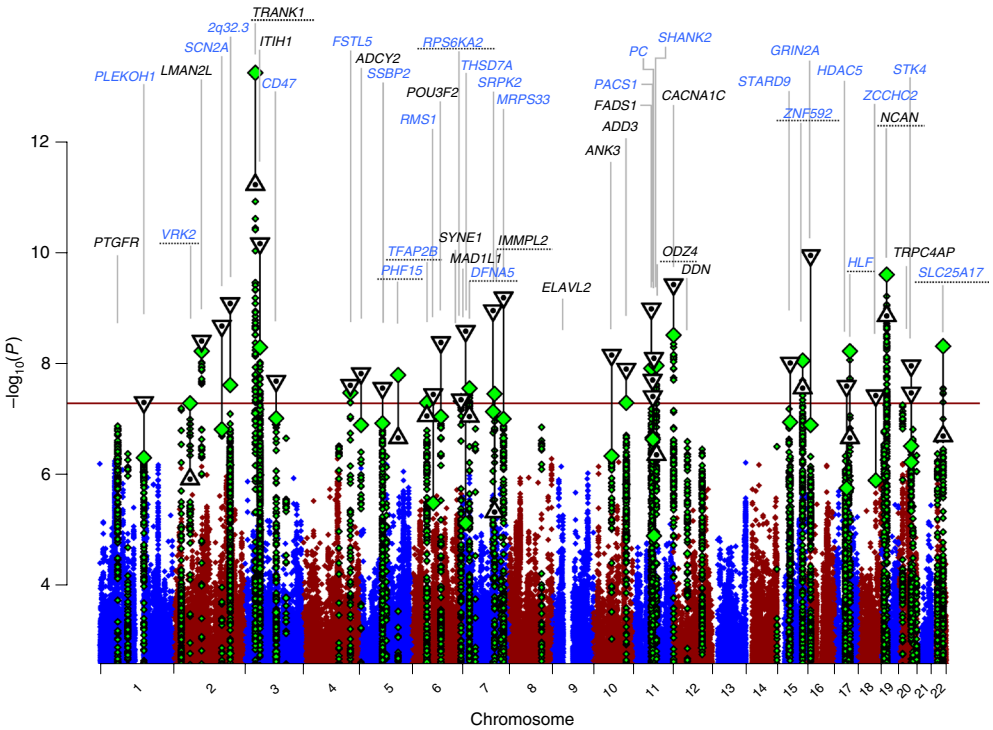

Fig. 1 | Manhattan plot for our primary genome-wide association analysis of 20,352 cases and 31,358 controls. GWAS $-\log_{10}P$ values are plotted for all SNPs across chromosomes 1–22 (diamonds, green for loci with lead SNP GWAS $P<10^{-6}$). Combined GWAS + follow-up $-\log_{10}P$ for lead SNPs reaching genome-wide significance in either GWAS or combined analysis (triangles, inverted if GWAS + follow-up $-\log_{10}P >$ GWAS $-\log_{10}P$). Labels correspond to gene symbols previously reported for published loci (black) and the nearest genes for newly identified loci (blue), at top if GWAS + follow-up $P<5\times10^{-8}$. Loci with one-tailed follow-up $P>0.05$ (Table 1) have dotted underlined locus names.

We conducted PRS analyses to explore the relationship between genetic risk of SCZ and DEPR, and BD subtypes and psychosis (Fig. 2 and Supplementary Table 13). PRS calculated from SCZ[31] were significantly higher in BD1 cases than in BD2 cases ($P=5.6\times10^{-17}$, P threshold = 0.1) and in cases with psychosis compared to those without psychosis ($P=2.12\times10^{-6}$, P threshold = 0.1). Conversely, PRS calculated from DEPR[33] were significantly higher in BD2 cases than in BD1 cases ($P=8.5\times10^{-10}$, P threshold = 0.01), independent of psychosis. Genetic correlations from LD score regression support these results; genetic correlations were greater for SCZ with BD1 ($r_g=0.71$, s.e.m. = 0.025) than with BD2 ($r_g=0.51$, s.e.m. = 0.072), and were greater for DEPR with BD2 ($r_g=0.69$, s.e.m. = 0.093) than with BD1 ($r_g=0.30$, s.e.m. = 0.028) (Supplementary Table 12).

Systems biology and in silico functional analyses. We tested for functional genomic enrichment in our BD GWAS using partitioned LD score regression and a range of functional annotations across tissues[45] (Supplementary Note and Supplementary Table 14). SNP-based BD heritability was most enriched in open chromatin annotations in the central nervous system (proportion SNPs = 0.14, proportion $h^2_{snp}=0.60$, enrichment = 3.8, $P=3\times10^{-14}$). We also used DEPICT[46] to test for expression of BD-associated genes across tissues, and found significant enrichment of central nervous system ($P<1.4\times10^{-3}$, false discovery rate (FDR) < 0.01) and neurosecretory system ($P=2.0\times10^{-6}$, FDR < 0.01) genes (Supplementary Table 15).

To prioritize genes that may play a functional role in BD, we integrated BD GWAS association statistics with eQTL (SNP–gene expression association) and mQTL (SNP–DNA methylation association) data using summary Mendelian randomization (SMR)[47–49] (Supplementary Table 16 and Supplementary Note). SMR identified 21 genes using eQTL data that were significant after multiple testing correction, without evidence of heterogeneity between GWAS and eQTL association signals. Association with *GNL3* was observed in both brain and blood, highlighting the utility of using blood eQTL data as proxy for brain eQTLs[49]. Methylation profiles at six CpGs in the brain and ten CpGs in the blood were associated with BD, four of which overlapped between brain and blood mQTL: *MUSTN1*, *GLT8D1*, *HAPLN4* and *FADS2*.

Finally, we used MAGMA[50] to conduct a gene-wise BD GWAS and to test for enrichment of pathways curated from multiple sources (see Supplementary Note). We note that significance levels were assigned to genes by physical proximity of SNPs, and do not imply that significant genes are causal for BD. Genic association results included 154 Bonferroni significant genes (MAGMA $P_{JOINT}<2.8\times10^{-6}$), including 82 genes in 20 genome-wide-significant loci, and 73 genes in 27 additional loci that did not reach genome-wide significance (Supplementary Table 17). Nine related pathways were significantly enriched for genes with BD associations ($P<7.0\times10^{-5}$, FDR < 0.05), including abnormal motor coordination/balance pathways (from mice), regulation of insulin secretion and endocannabinoid signaling (Supplementary Table 18 and Supplementary Fig. 7).

Discussion

We carried out a large bipolar disorder GWAS and identified 30 genome-wide-significant loci, including 20 that were newly identified. Previous BD GWAS have reported a total of 20 loci significantly associated with BD[9–23]; 12 of these previously reported loci were not genome-wide significant in our GWAS meta-analysis, but all had $P_{GWAS}\leq1.3\times10^{-5}$ (Supplementary Table 4c). Our recent GWAS of BD and SCZ[51], which included our discovery GWAS data jointly analyzed with published SCZ data[31] (without overlapping control subjects), highlighted similarities and differences in BD

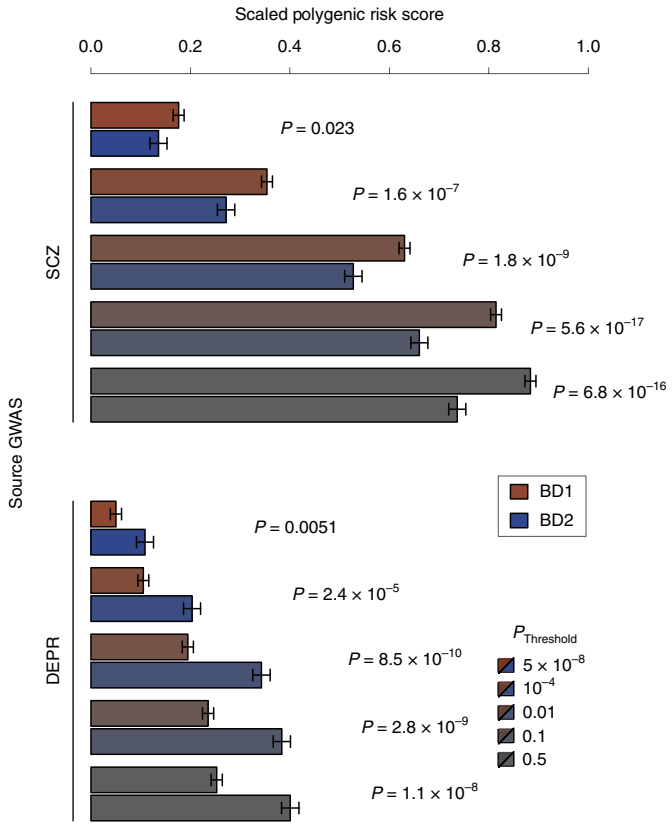

Fig. 2 | Association of BD1 and BD2 subtypes with SCZ and DEPR PRS. The mean PRS values (1 s.e.m. error bars) are shown, adjusted for study and ancestry covariates and scaled to the PRS mean and s.d. in control subjects, in BD1 (red) and BD2 (blue) cases, for increasing source GWAS *P* value thresholds (increasing gray) as indicated. *P* values (italics) test BD1 versus BD2 mean PRS, in logistic regression of case subtype on PRS with covariates. Results are detailed in Supplementary Table 13.

and SCZ in terms of known associated SNPs and PRS–subphenotype associations; here, we maximized power to identify BD associations. The phenotypic variance explained by PRS on the basis of our BD GWAS data is ~8% (observed scale; 4% on the liability scale[52]), an increase from 2.8% (1.2% on the liability scale) in our previous study[9]. The results of our BD subtype PRS analyses support the nosological distinction between BD1 and BD2, but also highlight the importance of psychosis beyond DSM subtypes, corroborating and expanding evidence from previous clinical[53] and genetic studies[51,54,55]. The DEPR versus BD PRS analyses provide further support for the distinction between BD1 and BD2, independent of the presence of psychosis.

Of the 19 loci identified in our discovery GWAS, only 11 were genome-wide significant in meta-analysis of our GWAS and follow-up samples. These results are not unexpected given the small effect sizes and the winner's curse[28,56] (Supplementary Note and Supplementary Fig. 4); SNPs can teeter-totter around the genome-wide-significance threshold even as sample sizes increase. Genetic heterogeneity observed among BD GWAS cohorts[8] could also contribute to inconsistent replication results; we observed variable polygenic effects between BD subtypes (Fig. 2 and Supplementary Table 13) as well as between cohorts in our study (Supplementary Fig. 2 and Supplementary Table 4) which used a diversity of criteria to define cases (Supplementary Note). Remarkably, the strongest association signal from the discovery GWAS, at the *TRANK1* locus (rs9834970; $P_{combined} = 5.7 \times 10^{-12}$, odds ratio, OR = 0.93), exhibited significant heterogeneity among discovery GWAS cohorts (Cochran's Q $P = 1.9 \times 10^{-4}$), and did not replicate in the follow-up sample (one-tailed $P_{follow\text{-}up} = 0.15$) (Supplementary Data 2 and 3). This locus has been significant in recent[11,12,17,18] but not earlier BD GWAS[9,13,20]. Thus, complex genetic architecture as well as phenotypic heterogeneity may contribute to the inconsistency of genome-wide-significant findings within and across BD GWAS studies. The observed heterogeneity is a major challenge for GWAS of psychiatric disorders and calls for careful and systematic clinical assessment of cases and controls in parallel with continued efforts to collect larger sample sizes.

Of the 30 BD-associated loci, 8 also harbor associations[31,32,57] with schizophrenia (SCZ); however, conditional analyses suggest that the BD and SCZ associations at three of the eight shared loci (in the *NCAN*, *TRANK1* and chr7q22.3:105 Mb loci) may be independent (Supplementary Table 9). Differential BD and SCZ associations may represent opportunities to understand the genetic distinctions between these closely related and sometimes clinically difficult to distinguish disorders. We did not find BD loci that overlap with those associated with major depression[33].

The confirmed association within loci containing *CACNA1C* and other voltage-gated calcium channel genes supports the rekindled interest in calcium channel antagonists as potential treatments for BD, with similar examination ongoing for other genes implicated in SCZ GWAS[58]. Other genes within novel BD-associated loci include those coding for other ion channels and transporters (*SCN2A*, *SLC4A1*), neurotransmitter receptors (*GRIN2A*) and synaptic components (*RIMS1*, *ANK3*). Further study will confirm whether or not these are the causal genes in the loci. These processes are important in neuronal hyperexcitability[59], an excess of which has been reported in induced pluripotent-stem-cell-derived neurons from patients with BD, and which has been shown to be affected by the classic mood-stabilizing drug lithium[60]. In addition, SMR eQTL and mQTL analyses implicate *GLT8D1*, which is involved in proliferation and differentiation of neural stem cells[61]. Pathway analyses reveal genetic evidence for insulin secretion and endocannabinoid signaling in BD. There is evidence of insulin action in the brain[62] and in BD[63]. The endocannabinoid system has possible roles in schizophrenia[64,65] and depression[66]. Top genes appearing in these pathways include calcium and potassium channel subunits, MAP kinase and GABA-A receptor subunit genes (Supplementary Table 18).

We observe significant positive genetic correlations with educational attainment, but not with either adult or childhood IQ, suggesting that the role of BD genetics in educational attainment may be independent of general intelligence. This result is inconsistent with suggestions from epidemiological studies[67], but in agreement with results from a recent clinical study[68].

In summary, findings from the genome-wide analysis of BD reveal an extensive polygenic genetic architecture of the disease, implicate brain calcium channels and neurotransmitter function in BD etiology, and confirm that BD is part of a spectrum of highly correlated psychiatric and mood disorders.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of code and data availability and associated accession codes are available at https://doi.org/10.1038/s41588-019-0397-8.

Received: 11 March 2018; Accepted: 18 March 2019;
Published online: 1 May 2019

References

1. Ferrari, A. J. et al. The prevalence and burden of bipolar disorder: findings from the global burden of disease study 2013. *Bipolar Disord.* **18**, 440–450 (2016).
2. Lichtenstein, P. et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234–239 (2009).

3. Edvardsen, J. et al. Heritability of bipolar spectrum disorders. Unity or heterogeneity? *J. Affect. Disord.* **106**, 229–240 (2008).
4. McGuffin, P. et al. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **60**, 497–502 (2003).
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Association Publishing, 2013).
6. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (World Health Organization, 1992).
7. Craddock, N. & Owen, M. J. The Kraepelinian dichotomy—going, going… but still not gone. *Br. J. Psychiatry* **196**, 92–95 (2010).
8. Lee, S. H. et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45**, 984–994 (2013).
9. Sklar, P. et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* **43**, 977–983 (2011).
10. Baum, A. E. et al. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol. Psychiatry* **13**, 197–207 (2008).
11. Charney, A. W. et al. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Transl. Psychiatry* **7**, e993 (2017).
12. Chen, D. T. et al. Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol. Psychiatry* **18**, 195–205 (2013).
13. Cichon, S. et al. Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *Am. J. Hum. Genet.* **88**, 372–381 (2011).
14. Ferreira, M. A. R. et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat. Genet.* **40**, 1056–1058 (2008).
15. Green, E. K. et al. Association at SYNE1 in both bipolar disorder and recurrent major depression. *Mol. Psychiatry* **18**, 614–617 (2013).
16. Green, E. K. et al. Replication of bipolar disorder susceptibility alleles and identification of two novel genome-wide significant associations in a new bipolar disorder case-control sample. *Mol. Psychiatry* **18**, 1302–1307 (2013).
17. Hou, L. et al. Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Hum. Mol. Genet.* **25**, 3383–3394 (2016).
18. Mühleisen, T. W. et al. Genome-wide association study reveals two new risk loci for bipolar disorder. *Nat. Commun.* **5**, 3339 (2014).
19. Schulze, T. G. et al. Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder. *Mol. Psychiatry* **14**, 487–491 (2009).
20. Scott, L. J. et al. Genome-wide association and meta-analysis of bipolar disorder in individuals of European ancestry. *Proc. Natl Acad. Sci. USA* **106**, 7501–7506 (2009).
21. Sklar, P. et al. Whole-genome association study of bipolar disorder. *Mol. Psychiatry* **13**, 558–569 (2008).
22. Smith, E. N. et al. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol. Psychiatry* **14**, 755–763 (2009).
23. Burton, P. R. et al. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).
24. Gratten, J., Wray, N. R., Keller, M. C. & Visscher, P. M. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nat. Neurosci.* **17**, 782–790 (2014).
25. Bulik-Sullivan, B. K. et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
26. Zheng, J. et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* **33**, 272–279 (2017).
27. Palmer, C. & Pe'er, I. Statistical correction of the winner's curse explains replication variability in quantitative trait genome-wide association studies. *PLoS Genet.* **13**, e1006916 (2017).
28. Zhong, H. & Prentice, R. L. Bias-reduced estimators and confidence intervals for odds ratios in genome-wide association studies. *Biostatistics* **9**, 621–634 (2008).
29. Holland, D. et al. Beyond SNP heritability: polygenicity and discoverability estimated for multiple phenotypes with a univariate gaussian mixture model. Preprint at *bioRXiv* https://doi.org/10.1101/133132 (2018).
30. Gao, X., Starmer, J. & Martin, E. R. A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms. *Genet. Epidemiol.* **32**, 361–369 (2008).
31. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
32. Ripke, S. et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* **45**, 1150–1159 (2013).
33. Wray, N. R. et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* **50**, 668–681 (2018).
34. Okbay, A. et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat. Genet.* **48**, 624–633 (2016).
35. Cross-Disorder Group of the Psychiatric Genomics Consortium et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45**, 984–994 (2013).
36. Duncan, L. et al. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. *Am. J. Psychiatry* **174**, 850–858 (2017).
37. Otowa, T. et al. Meta-analysis of genome-wide association studies of anxiety disorders. *Mol. Psychiatry* **21**, 1391–1399 (2016).
38. Gale, C. R. et al. Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank. *Transl. Psychiatry* **6**, e791 (2016).
39. Rietveld, C. A. et al. GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* **340**, 1467–1471 (2013).
40. Okbay, A. et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539–542 (2016).
41. Benyamin, B. et al. Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Mol. Psychiatry* **19**, 253–258 (2014).
42. Sniekers, S. et al. Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat. Genet.* **49**, 1107–1112 (2017).
43. MacArthur, J. et al. The new NHGRI-EBI catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res.* **45**, D896–D901 (2017).
44. Ikeda, M. et al. A genome-wide association study identifies two novel susceptibility loci and trans population polygenicity associated with bipolar disorder. *Mol. Psychiatry* **23**, 639–647 (2018).
45. Finucane, H. K. et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
46. Pers, T. H. et al. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6**, 5890 (2015).
47. Zhu, Z. et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).
48. Pavlides, J. M. W. et al. Predicting gene targets from integrative analyses of summary data from GWAS and eQTL studies for 28 human complex traits. *Genome Med.* **8**, 84 (2016).
49. Qi, T. et al. Identifying gene targets for brain-related traits using transcriptomic and methylomic data from blood. *Nat. Commun.* **9**, 2282 (2018).
50. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
51. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell* **173**, 1705–1715.e16 (2018).
52. Lee, S. H., Goddard, M. E., Wray, N. R. & Visscher, P. M. A better coefficient of determination for genetic profile analysis. *Genet. Epidemiol.* **36**, 214–224 (2012).
53. Simonsen, C. et al. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. *Schizophr. Bull.* **37**, 73–83 (2011).
54. Goes, F. S. et al. Genome-wide association of mood-incongruent psychotic bipolar disorder. *Transl. Psychiatry* **2**, e180 (2012).
55. Allardyce, J. et al. Association between schizophrenia-related polygenic liability and the occurrence and level of mood-incongruent psychotic symptoms in bipolar disorder. *JAMA Psychiatry* **75**, 28–35 (2018).
56. Palmer, C. & Pe'er, I. Statistical correction of the winner's curse explains replication variability in quantitative trait genome-wide association studies. *PLoS Genet.* **13**, e1006916 (2017).
57. Goes, F. S. et al. Genome-wide association study of schizophrenia in Ashkenazi Jews. *Am. J. Med. Genet. B* **168**, 649–659 (2015).
58. Gaspar, H. A. & Breen, G. Drug enrichment and discovery from schizophrenia genome-wide association results: an analysis and visualisation approach. *Sci. Rep.* **7**, 12460 (2017).
59. Camandola, S. & Mattson, M. P. Aberrant subcellular neuronal calcium regulation in aging and alzheimer's disease. *Biochim. Biophys. Acta Mol. Cell Res.* **1813**, 965–973 (2011).

60. Mertens, J. et al. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* **527**, 95–99 (2015).
61. Yang, C.-P. et al. Comprehensive integrative analyses identify GLT8D1 and CSNK2B as schizophrenia risk genes. *Nat. Commun.* **9**, 838 (2018).
62. Lee, S.-H., Zabolotny, J. M., Huang, H., Lee, H. & Kim, Y.-B. Insulin in the nervous system and the mind: functions in metabolism, memory, and mood. *Mol. Metab.* **5**, 589–601 (2016).
63. McIntyre, R. S. et al. A randomized, double-blind, controlled trial evaluating the effect of intranasal insulin on neurocognitive function in euthymic patients with bipolar disorder. *Bipolar Disord.* **14**, 697–706 (2012).
64. Desfossés, J., Stip, E., Bentaleb, L. A. & Potvin, S. Endocannabinoids and schizophrenia. *Pharmaceuticals* **3**, 3101–3126 (2010).
65. Zamberletti, E., Rubino, T. & Parolaro, D. The endocannabinoid system and schizophrenia: integration of evidence. *Curr. Pharm. Des.* **18**, 4980–4990 (2012).
66. Serra, G. & Fratta, W. A possible role for the endocannabinoid system in the neurobiology of depression. *Clin. Pract. Epidemiol. Ment. Health* **3**, 25 (2007).
67. MacCabe, J. H. et al. Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. *Br. J. Psychiatry* **196**, 109–115 (2010).
68. Vreeker, A. et al. High educational performance is a distinctive feature of bipolar disorder: a study on cognition in bipolar disorder, schizophrenia patients, relatives and controls. *Psychol. Med.* **46**, 807–818 (2016).

Acknowledgements

This paper is dedicated to the memory of Psychiatric Genomics Consortium (PGC) founding member and Bipolar Disorder Working Group co-chair Pamela Sklar. We thank the participants who donated their time, experiences and DNA to this research, and the clinical and scientific teams that worked with them. We are deeply indebted to the investigators who comprise the PGC. Analyses were carried out on the NL Genetic Cluster Computer (http://www.geneticcluster.org), hosted by SURFsara, and the Mount Sinai high performance computing cluster (http://hpc.mssm.edu). PGC members have received major funding from the US National Institute of Mental Health. This work was funded in part by the Brain and Behavior Research Foundation, Stanley Medical Research Institute, University of Michigan, Pritzker Neuropsychiatric Disorders Research Fund L.L.C., Marriot Foundation and the Mayo Clinic Center for Individualized Medicine, the NIMH Intramural Research Program; Canadian Institutes of Health Research; the UK Maudsley NHS Foundation Trust, NIHR, NRS, MRC, Wellcome Trust; European Research Council; German Ministry for Education and Research, German Research Foundation IZKF of Münster, Deutsche Forschungsgemeinschaft, ImmunoSensation, the Dr Lisa-Oehler Foundation, University of Bonn; the Swiss National Science Foundation; French Foundation FondaMental and ANR; Spanish Ministerio de Economía, CIBERSAM, Industria y Competitividad, European Regional Development Fund (ERDF), Generalitat de Catalunya, EU Horizon 2020 Research and Innovation Programme; BBMRI-NL; South-East Norway Regional Health Authority and Mrs Throne-Holst; Swedish Research Council, Stockholm County Council, Söderström Foundation; Lundbeck Foundation, Aarhus University; Australia NHMRC, NSW Ministry of Health, Janette M. O'Neil and Betty C. Lynch. The views expressed are those of the authors and not necessarily those of their institutions or any funding or regulatory bodies. Additional acknowledgements, including funding sources, are presented in the Supplementary Note.

Author contributions

Writing group: E.A.S., G.B., A.J.F., A. McQuillin, S.R., J.R.I.C., N.M., N.R.W., A.D.F., H.J.E., S.C., R.A.O., L.J.S., O.A.A. and J.K. **PGC BD principal investigator group:** E.A.S., G.B., A.J.F., A. McQuillin, D. Curtis, R.H.P., R.A., I.A., M.A., L.B., B.T.B., F.B., W.H.B., J.M.B., D.H.R.B., M. Boehnke, A.D.B., A.C., N.C., U.D., T. Esko, B.E., M. Frye, J.M.F., E.S.G., M.G., F.G., M.G.-S., J.H., D.M.H., C.M.H., I.J., L.A.J., R.S.K., M. Landén, M. Leboyer, C.M.L., Q.S.L., J. Lissowska, N.G.M., S.L.M., A.M.M., F.J.M., I.M., A. Metspalu, P.B. Mitchell, G.M., O.M., P.B. Mortensen, B.M.-M., R.M.M., B.M.N., V.N., M.N., M.M.N., M.C.O'D., K.J.O., M.J.O., S.A.P., C.P., M.T.P., J.A.R.-Q., M. Ribasés, M. Rietschel, G.A.R., M. Schalling, P.R.S., T.G.S., A.S., J.W.S., H.S., K.S., E. Stordal, G.T., A.E.V., E.V., J.B.V., T.W., J.I.N., A.D.F., H.J.E., S.C., R.A.O., L.J.S., O.A.A., J.K. and P.S. **Bioinformatics:** E.A.S., G.B., A.J.F., J.R.I.C., H.A.G., P.A.H., S.E.B., D.W.C., V.E.-P., C.G., M.L.H., S.H., R. Karlsson, M. Leber, C. Liu, F. Meng, L.M.O.L., A.P.S.O., C.S.R., P.R., P.D.S., M. Steffens, S. Szelinger, T.E.T., S.X., P. Zandi, eQTLGen Consortium, BIOS Consortium, T. Esko, E.S.G., Q.S.L., G.A.R. and H.S. **Clinical:** A. McQuillin, M.M., E.A., N.A.-R., A.A., N.B., M. Bauer, C.B.P., E.B., M.P.B., M. Budde, M. Burmeister, W. Byerley, M.C., P.C., W.C., D. Curtis, P.M.C., J.R.D., T. Elvsåshagen, L. Forty, C.F., K.G., J. Garnham, M.G.P., K.G.-S., M.J.G., J. Grove, J.G.-P., M. Hautzinger, U.H., M. Hipolito, A.J., J.L.K., S.K.-S., M.K., R. Kupka, C. Lavebratt, J. Lawrence, W.B.L., S.L., D.J.M., P.B. Mahon, W.M., L. Martinsson, P.M., M.G.M., H.M., A.N.A., E.A.N., C.O'D., L.O., U.Ö., R.H.P., A. Perry, A. Pfennig, J.B.P., E.J.R., A.R., J.P.R., F.R., M. Rivera, W.A.S., C.S.W., E. Sigurdsson, C.S., O.B.S., J.L.S., A.T.S., D.S.C., J.S.S., F.S., J.S., R.C.T., H.V., T.W.W., A.H.Y., R.A., I.A., M.A., B.T.B., F.B., D.H.R.B., A.D.B., A.C., N.C., U.D., B.E., M. Frye, E.S.G., M.G., F.G., M.G.-S., J.H., I.J., L.A.J., R.S.K., G.K., M. Landén, J. Lissowska, N.G.M., F. Mayoral, S.L.M., A.M.M., F.J.M., I.M., P.B. Mitchell, G.M., O.M., P.B. Mortensen, V.N., M.C.O'D., K.J.O., M.J.O., C.P., M.T.P., J.A.R.-Q., M. Rietschel, T.G.S., A.S., J.W.S., E. Stordal, A.E.V., E.V., J.I.N. and A.D.F. **Genomic assays/data generation:** G.B., A.J.F., E.A., D.A., M.B.-H., C.B.P., J.B.-G., T.-K.C., D.W.C., C. Cruceanu, F.D., J.D.-F., S.D., S.B.F., J.F., M.G.P., E.K.G., P.H., S.J., R. Kandaswamy, A.C.K., S.E.L., A. Maaser, J.D.M., L. Milani, G.W.M., D.W.M., T.W.M., E.R., C.S.-M., T.S., C.S.H., S. Szelinger, J.T., S.H.W., P. Zhang, A.C., T. Esko, J.M.F., E.S.G., M.G., D.M.H., R.M.M., M.M.N., M. Ribasés, G.A.R., G.T. and S.C. **Obtained funding for BD samples:** G.B., H.A., N.A.-R., J.D.B., W. Bunney, J.R.D., N.B.F., L. Frisén, M.J.G., S.J., J.A.K., C. Lavebratt, S.L., P.M., G.W.M., U.Ö., J.B.P., M. Rivera, A.F.S., C.S.W., S.J.W., T.W.W., A.H.Y., M.A., B.T.B., W.H.B., J.M.B., M.Boehnke, A.D.B., A.C., N.C., M. Frye, J.M.F., E.S.G., M.G., M.G.-S., I.J., L.A.J., M. Landén, M. Leboyer, C.M.L., N.G.M., A. Metspalu, P.B. Mitchell, O.M., P.B. Mortensen, B.M.N., M.N., M.M.N., M.C.O'D., M.J.O., C.P., M.T.P., M. Rietschel, G.A.R., P.R.S., T.G.S., J.W.S., G.T., J.B.V., T.W., J.I.N., H.J.E., R.A.O. and P.S. **Statistical analysis:** E.A.S., G.B., S.R., V.T., M.M., Y.W., J.R.I.C., H.A.G., C.A.d.L., S. Steinberg, J.M.W.P., M.T., E.M.B., T.H.P., P.A.H., A.L.R., L.A., N.A.-R., T.D.A., V.A., S.A., J.A.B., R.B., S.E.B., J.B., F.C., K.C., A.W.C., D. Chen, C. Churchhouse, A.M.D., S.d.J., A.L.D., A.D., V.E.-P., C.C.F., M. Flickinger, T.M.F., D.G., C.G., J. Goldstein, S.D.G., T.A.G., J. Grove, W.G., M.L.H., D.H., L.H., J.S.J., R. Karlsson, M. Leber, P.H.L., J.Z.L., S.M., S.E.M., D.W.M., N.M., H.N., C.M.N., L.M.O.L., A.P.S.O., S.M.P., C.S.R., P.R., D.M.R., N.J.S., O.B.S., T.E.T., W.W., W.X., P. Zandi, P. Zhang, S.Z., eQTLGen Consortium, BIOS Consortium, J.M.B., A.D.B., M.J.D., E.S.G., F.G., Q.S.L., B.M.-M., D.P., H.S., P.F.S., N.R.W. and P.S.

Competing interests

T.E.T., S. Steinberg, H.S. and K.S. are employed by deCODE Genetics/Amgen. Multiple additional authors work for pharmaceutical or biotechnology companies in a manner directly analogous to academic co-authors and collaborators. A.H.Y. has given paid lectures and is on advisory boards for the following companies with drugs used in affective and related disorders: Astra Zeneca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier, Livanova. A.H.Y. is Lead Investigator for Embolden Study (Astra Zeneca), BCI Neuroplasticity Study and Aripiprazole Mania Study, which are investigator-initiated studies from Astra Zeneca, Eli Lilly, Lundbeck and Wyeth. J.N. is an investigator for Janssen. P.F.S. reports the following potentially competing interests: Lundbeck (advisory committee), Pfizer (Scientific Advisory Board member) and Roche (grant recipient, speaker reimbursement). G.B. reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly. O.A.A. has received speaker fees from Lundbeck. J.A.R.-Q. was on the speakers' bureau and/or acted as consultant for Eli Lilly, Janssen-Cilag, Novartis, Shire, Lundbeck, Almirall, Braingaze, Sincrolab and Rubió in the last 5 years. He also received travel awards (air tickets and hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire and Eli Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious and Rubió. E.V. has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, Astra Zeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Catalan Government (AGAUR and PERIS), the Spanish Ministry of Science, Innovation, and Universities (AES and CIBERSAM), the Seventh European Framework Programme and Horizon 2020 and the Stanley Medical Research Institute. T. Elvsåshagen has received speaker fees from Lundbeck. All other authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41588-019-0397-8.

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence and requests for materials should be addressed to E.A.S. or J.K.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Eli A. Stahl[1,2,3,205*], Gerome Breen[4,5,205], Andreas J. Forstner[6,7,8,9,10,205], Andrew McQuillin[11,205], Stephan Ripke[12,13,14,205], Vassily Trubetskoy[13], Manuel Mattheisen[15,16,17,18,19], Yunpeng Wang[20,21], Jonathan R. I. Coleman[4,5], Héléna A. Gaspar[4,5], Christiaan A. de Leeuw[22], Stacy Steinberg[23], Jennifer M. Whitehead Pavlides[24], Maciej Trzaskowski[25], Enda M. Byrne[25], Tune H. Pers[3,26], Peter A. Holmans[27], Alexander L. Richards[27], Liam Abbott[12], Esben Agerbo[19,28], Huda Akil[29], Diego Albani[30], Ney Alliey-Rodriguez[31], Thomas D. Als[15,16,19], Adebayo Anjorin[32], Verneri Antilla[14], Swapnil Awasthi[13], Judith A. Badner[33], Marie Bækvad-Hansen[19,34], Jack D. Barchas[35], Nicholas Bass[11], Michael Bauer[36], Richard Belliveau[12], Sarah E. Bergen[37], Carsten Bøcker Pedersen[19,28], Erlend Bøen[38], Marco P. Boks[39], James Boocock[40], Monika Budde[41], William Bunney[42], Margit Burmeister[43], Jonas Bybjerg-Grauholm[19,34], William Byerley[44], Miquel Casas[45,46,47,48], Felecia Cerrato[12], Pablo Cervantes[49], Kimberly Chambert[12], Alexander W. Charney[2], Danfeng Chen[12], Claire Churchhouse[12,14], Toni-Kim Clarke[50], William Coryell[51], David W. Craig[52], Cristiana Cruceanu[49,53], David Curtis[54,55], Piotr M. Czerski[56], Anders M. Dale[57,58,59,60], Simone de Jong[4,5], Franziska Degenhardt[8], Jurgen Del-Favero[61], J. Raymond DePaulo[62], Srdjan Djurovic[63,64], Amanda L. Dobbyn[1,2], Ashley Dumont[12], Torbjørn Elvsåshagen[65,66], Valentina Escott-Price[27], Chun Chieh Fan[60], Sascha B. Fischer[6,10], Matthew Flickinger[67], Tatiana M. Foroud[68], Liz Forty[27], Josef Frank[69], Christine Fraser[27], Nelson B. Freimer[70], Louise Frisén[71,72,73], Katrin Gade[41,74], Diane Gage[12], Julie Garnham[75], Claudia Giambartolomei[76], Marianne Giørtz Pedersen[19,28], Jaqueline Goldstein[12], Scott D. Gordon[77], Katherine Gordon-Smith[78], Elaine K. Green[79], Melissa J. Green[80,81], Tiffany A. Greenwood[59], Jakob Grove[15,16,19,82], Weihua Guan[83], José Guzman-Parra[84], Marian L. Hamshere[27], Martin Hautzinger[85], Urs Heilbronner[41], Stefan Herms[6,8,10], Maria Hipolito[86], Per Hoffmann[6,8,10], Dominic Holland[57,87], Laura Huckins[1,2], Stéphane Jamain[88,89], Jessica S. Johnson[1,2], Anders Juréus[37], Radhika Kandaswamy[4], Robert Karlsson[37], James L. Kennedy[90,91,92,93], Sarah Kittel-Schneider[94], James A. Knowles[95,96], Manolis Kogevinas[97], Anna C. Koller[8], Ralph Kupka[98,99,100], Catharina Lavebratt[71], Jacob Lawrence[101], William B. Lawson[86], Markus Leber[102], Phil H. Lee[12,14,103], Shawn E. Levy[104], Jun Z. Li[105], Chunyu Liu[106], Susanne Lucae[107], Anna Maaser[8], Donald J. MacIntyre[108,109], Pamela B. Mahon[62,110], Wolfgang Maier[111], Lina Martinsson[72], Steve McCarroll[12,112], Peter McGuffin[4], Melvin G. McInnis[113], James D. McKay[114], Helena Medeiros[96], Sarah E. Medland[77], Fan Meng[29,113], Lili Milani[115], Grant W. Montgomery[25], Derek W. Morris[116,117], Thomas W. Mühleisen[6,118], Niamh Mullins[4], Hoang Nguyen[1,2], Caroline M. Nievergelt[59,119], Annelie Nordin Adolfsson[120], Evaristus A. Nwulia[86], Claire O'Donovan[75], Loes M. Olde Loohuis[70], Anil P. S. Ori[70], Lilijana Oruc[121], Urban Ösby[122], Roy H. Perlis[123,124], Amy Perry[78], Andrea Pfennig[36], James B. Potash[62], Shaun M. Purcell[2,110], Eline J. Regeer[125], Andreas Reif[94], Céline S. Reinbold[6,10], John P. Rice[126], Fabio Rivas[84], Margarita Rivera[4,127], Panos Roussos[1,2,128], Douglas M. Ruderfer[129], Euijung Ryu[130], Cristina Sánchez-Mora[45,46,48], Alan F. Schatzberg[131], William A. Scheftner[132], Nicholas J. Schork[133], Cynthia Shannon Weickert[80,81], Tatyana Shehktman[59], Paul D. Shilling[59], Engilbert Sigurdsson[134], Claire Slaney[75], Olav B. Smeland[135,136], Janet L. Sobell[137], Christine Søholm Hansen[19,34], Anne T. Spijker[138], David St Clair[139], Michael Steffens[140], John S. Strauss[92,141], Fabian Streit[69], Jana Strohmaier[69], Szabolcs Szelinger[142], Robert C. Thompson[113], Thorgeir E. Thorgeirsson[23], Jens Treutlein[69], Helmut Vedder[143], Weiqing Wang[1,2], Stanley J. Watson[113], Thomas W. Weickert[80,81], Stephanie H. Witt[69], Simon Xi[144], Wei Xu[145,146], Allan H. Young[147], Peter Zandi[148], Peng Zhang[149], Sebastian Zöllner[113], eQTLGen Consortium[150], BIOS Consortium[150], Rolf Adolfsson[120], Ingrid Agartz[17,38,151], Martin Alda[75,152], Lena Backlund[72], Bernhard T. Baune[153,154],

Frank Bellivier[155,156,157,158], Wade H. Berrettini[159], Joanna M. Biernacka[130], Douglas H. R. Blackwood[50], Michael Boehnke[67], Anders D. Børglum[15,16,19], Aiden Corvin[117], Nicholas Craddock[27], Mark J. Daly[12,14], Udo Dannlowski[154], Tõnu Esko[3,112,115,160], Bruno Etain[155,157,158,161], Mark Frye[162], Janice M. Fullerton[81,163], Elliot S. Gershon[31,164], Michael Gill[117], Fernando Goes[62], Maria Grigoroiu-Serbanescu[165], Joanna Hauser[56], David M. Hougaard[19,34], Christina M. Hultman[37], Ian Jones[27], Lisa A. Jones[78], René S. Kahn[2,39], George Kirov[27], Mikael Landén[37,166], Marion Leboyer[89,155,167], Cathryn M. Lewis[4,5,168], Qingqin S. Li[169], Jolanta Lissowska[170], Nicholas G. Martin[77,171], Fermin Mayoral[84], Susan L. McElroy[172], Andrew M. McIntosh[50,173], Francis J. McMahon[174], Ingrid Melle[175], Andres Metspalu[115,176], Philip B. Mitchell[80], Gunnar Morken[177,178], Ole Mors[19,179], Preben Bo Mortensen[15,19,28], Bertram Müller-Myhsok[53,180,181], Richard M. Myers[104], Benjamin M. Neale[3,12,14], Vishwajit Nimgaonkar[182], Merete Nordentoft[19,183], Markus M. Nöthen[8], Michael C. O'Donovan[27], Ketil J. Oedegaard[184,185], Michael J. Owen[27], Sara A. Paciga[186], Carlos Pato[96,187], Michele T. Pato[96], Danielle Posthuma[22,188], Josep Antoni Ramos-Quiroga[45,46,47,48], Marta Ribasés[45,46,48], Marcella Rietschel[69], Guy A. Rouleau[189,190], Martin Schalling[71], Peter R. Schofield[81,163], Thomas G. Schulze[41,62,69,74,174], Alessandro Serretti[191], Jordan W. Smoller[12,192,193], Hreinn Stefansson[23], Kari Stefansson[23,134], Eystein Stordal[194,195], Patrick F. Sullivan[37,196,197], Gustavo Turecki[198], Arne E. Vaaler[199], Eduard Vieta[200], John B. Vincent[141], Thomas Werge[19,201,202], John I. Nurnberger[203], Naomi R. Wray[24,25], Arianna Di Florio[27,197], Howard J. Edenberg[204], Sven Cichon[6,8,10,118], Roel A. Ophoff[39,40,70], Laura J. Scott[67], Ole A. Andreassen[135,136], John Kelsoe[59,206*], Pamela Sklar[1,2,205,206] and the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium[150]

[1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [2]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. [4]MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK. [5]NIHR BRC for Mental Health, King's College London, London, UK. [6]Department of Biomedicine, University of Basel, Basel, Switzerland. [7]Department of Psychiatry (UPK), University of Basel, Basel, Switzerland. [8]Institute of Human Genetics, University of Bonn School of Medicine & University Hospital Bonn, Bonn, Germany. [9]Centre for Human Genetics, University of Marburg, Marburg, Germany. [10]Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. [11]Division of Psychiatry, University College London, London, UK. [12]Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA. [13]Department of Psychiatry and Psychotherapy, Charité–Universitätsmedizin, Berlin, Germany. [14]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [15]iSEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, Denmark. [16]Department of Biomedicine–Human Genetics, Aarhus University, Aarhus, Denmark. [17]Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. [18]Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany. [19]iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark. [20]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen, Denmark. [21]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [22]Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. [23]deCODE Genetics/Amgen, Reykjavik, Iceland. [24]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia. [25]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia. [26]Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, USA. [27]Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, England. [28]National Centre for Register-based Research and Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark. [29]Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA. [30]Department of Neuroscience, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy. [31]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. [32]Department of Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, UK. [33]Department of Psychiatry, Rush University Medical Center, Chicago, IL, USA. [34]Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark. [35]Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA. [36]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. [37]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [38]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway. [39]Psychiatry, UMC Utrecht Brain Center Rudolf Magnus, Utrecht, the Netherlands. [40]Human Genetics, University of California, Los Angeles, Los Angeles, CA, USA. [41]Institute of Psychiatric Phenomics and Genomics, University Hospital, LMU Munich, Munich, Germany. [42]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA. [43]Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, USA. [44]Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA. [45]Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, Spain. [46]Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, Spain. [47]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. [48]Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut, Universitat Autònoma de Barcelona, Barcelona, Spain. [49]Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, Quebec, Canada. [50]Division of

Psychiatry, University of Edinburgh, Edinburgh, Scotland. [51]University of Iowa Hospitals and Clinics, Iowa City, IA, USA. [52]Translational Genomics, USC, Phoenix, AZ, USA. [53]Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany. [54]Centre for Psychiatry, Queen Mary University of London, London, UK. [55]UCL Genetics Institute, University College London, London, UK. [56]Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland. [57]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA. [58]Department of Radiology, University of California, San Diego, La Jolla, CA, USA. [59]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA. [60]Department of Cognitive Science, University of California, San Diego, La Jolla, CA, USA. [61]Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium. [62]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [63]Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, Norway. [64]NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway. [65]Department of Neurology, Oslo University Hospital, Oslo, Norway. [66]NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway. [67]Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA. [68]Department of Medical & Molecular Genetics, Indiana University, Indianapolis, IN, USA. [69]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. [70]Center for Neurobehavioral Genetics, University of California, Los Angeles, Los Angeles, CA, USA. [71]Department of Molecular Medicine and Surgery, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. [72]Department of Clinical Neuroscience, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. [73]Child and Adolescent Psychiatry Research Center, Stockholm, Sweden. [74]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany. [75]Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada. [76]Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA, USA. [77]Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [78]Department of Psychological Medicine, University of Worcester, Worcester, UK. [79]School of Biomedical Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, University of Plymouth, Plymouth, UK. [80]School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia. [81]Neuroscience Research Australia, Sydney, New South Wales, Australia. [82]Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. [83]Biostatistics, University of Minnesota System, Minneapolis, MN, USA. [84]Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, Spain. [85]Department of Psychology, Eberhard Karls Universität Tübingen, Tubingen, Germany. [86]Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC, USA. [87]Center for Multimodal Imaging and Genetics, University of California, San Diego, La Jolla, CA, USA. [88]Psychiatrie Translationnelle, Inserm U955, Créteil, France. [89]Faculté de Médecine, Université Paris Est, Créteil, France. [90]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Onatario, Canada. [91]Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. [92]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. [93]Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada. [94]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany. [95]Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [96]Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [97]ISGlobal, Barcelona, Spain. [98]Psychiatry, Altrecht, Utrecht, the Netherlands. [99]Psychiatry, GGZ inGeest, Amsterdam, the Netherlands. [100]Psychiatry, VU Medisch Centrum, Amsterdam, the Netherlands. [101]Department of, rth East London NHS Foundation Trust, Ilford, UK. [102]Department of Neurodegenerative Diseases and Geropsychiatry, University Hospital Bonn, Bonn, Germany. [103]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [104]HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA. [105]Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA. [106]Department of Psychiatry, University of Illinois at Chicago College of Medicine, Chicago, IL, USA. [107]Max Planck Institute of Psychiatry, Munich, Germany. [108]Mental Health, NHS 24, Glasgow, UK. [109]Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK. [110]Department of Psychiatry, Brigham and Women's Hospital, Boston, MA, USA. [111]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany. [112]Department of Genetics, Harvard Medical School, Boston, MA, USA. [113]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA. [114]Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, France. [115]Estonian Genome Center, University of Tartu, Tartu, Estonia. [116]Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, National University of Ireland, Galway, Galway, Ireland. [117]Neuropsychiatric Genetics Research Group, Department of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland. [118]Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany. [119]Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA. [120]Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, Sweden. [121]Department of Clinical Psychiatry, Psychiatry Clinic, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina. [122]Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. [123]Department of Psychiatry, Harvard Medical School, Boston, MA, USA. [124]Division of Clinical Research, Massachusetts General Hospital, Boston, MA, USA. [125]Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, the Netherlands. [126]Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, USA. [127]Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain. [128]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [129]Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA. [130]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. [131]Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA. [132]Rush University Medical Center, Chicago, IL, USA. [133]Scripps Translational Science Institute, La Jolla, CA, USA. [134]Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, Iceland. [135]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [136]NORMENT, University of Oslo, Oslo, Norway. [137]Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, USA. [138]Mood Disorders, PsyQ, Rotterdam, the Netherlands. [139]Institute for Medical Sciences, University of Aberdeen, Aberdeen, UK. [140]Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany. [141]Centre for Addiction and Mental Health, Toronto, Onatario, Canada. [142]Neurogenomics, TGen, Phoenix, AZ, USA. [143]Department of Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany. [144]Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA. [145]Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, Onatario, Canada. [146]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada. [147]Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK. [148]Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA. [149]Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [150]A list of members and affiliations appears in the Supplementary Note. [151]NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, Norway. [152]National Institute of Mental Health, Klecany, Czech Republic. [153]Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia. [154]Department of Psychiatry, University of Munster, Munster, Germany. [155]Department of Psychiatry and Addiction Medicine, Assistance Publique–Hopitaux de Paris, Paris, France. [156]Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, France. [157]UMR-S1144 Team 1: Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, France. [158]Department of Psychiatry, Université Paris Diderot, Paris, France. [159]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. [160]Division of Endocrinology, Children's Hospital Boston, Boston, MA, USA. [161]Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, UK. [162]Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA. [163]School of

Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia. [164]Department of Human Genetics, University of Chicago, Chicago, IL, USA. [165]Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania. [166]Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden. [167]INSERM, Paris, France. [168]Department of Medical & Molecular Genetics, King's College London, London, UK. [169]Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA. [170]Cancer Epidemiology and Prevention, M. Sklodowska–Curie Cancer Center and Institute of Oncology, Warsaw, Poland. [171]School of Psychology, The University of Queensland, Brisbane, Queensland, Australia. [172]Research Institute, Lindner Center of HOPE, Mason, OH, USA. [173]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. [174]Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA. [175]Division of Mental Health and Addiction and Institute of Clinical Medicine, Oslo University Hospital and University of Oslo, Oslo, Norway. [176]Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia. [177]Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology–NTNU, Trondheim, Norway. [178]Department of Psychiatry, St Olavs University Hospital, Trondheim, Norway. [179]Psychosis Research Unit, Aarhus University Hospital, Risskov, Denmark. [180]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [181]University of Liverpool, Liverpool, UK. [182]Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA. [183]Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, Denmark. [184]Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, Norway. [185]Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway. [186]Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA. [187]College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [188]Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, the Netherlands. [189]Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, Quebec, Canada. [190]Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada. [191]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy. [192]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [193]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [194]Department of Psychiatry, Hospital Namsos, Namsos, Norway. [195]Department of Mental Health, Norwegian University of Science and Technology, Trondheim, Norway. [196]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [197]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [198]Department of Psychiatry, McGill University, Montreal, Quebec, Canada. [199]Department of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway. [200]Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain. [201]Institute of Biological Psychiatry, MHC Sct. Hans, Mental Health Services Copenhagen, Roskilde, Denmark. [202]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [203]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA. [204]Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA. [205]Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [205]These authors contributed equally: Eli A Stahl, Gerome Breen, Andreas J Forstner, Andrew McQuillin, Stephan Ripke. [206]These authors jointly supervised this work: John Kelsoe, Pamela Sklar. *e-mail: eli.stahl@mssm.edu; jkelsoe@ucsd.edu

Methods

GWAS and follow-up cohorts. Our discovery GWAS sample comprises 32 cohorts from 14 countries in Europe, North America and Australia (Supplementary Table 1a), totaling 20,352 cases and 31,358 controls of European descent. A selected set of variants (see 'Follow-up cohort analysis') were tested in seven follow-up cohorts of European descent (Supplementary Table 1b), totaling 9,025 cases and 142,824 controls (N_{eff} = 23,991). The Supplementary Note summarizes the source and inclusion/exclusion criteria for cases and controls for each cohort. All cohorts in the initial PGC BD paper were included[9]. Cases were required to meet international consensus criteria (DSM-IV or ICD-10) for a lifetime diagnosis of BD established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists or medical record review. In most cohorts, controls were screened for the absence of lifetime psychiatric disorders and randomly selected from the population.

GWAS cohort analysis. We tested 20 principal components for association with BD using logistic regression; seven were significantly associated with phenotype and used in GWAS association analysis (principal components 1–6, 19). In each cohort, we performed logistic regression association tests for BD with imputed marker dosages including seven principal components to control for population stratification. For all GWAS cohorts, X-chromosome association analyses were conducted separately by sex and then meta-analyzed across sexes. We also conducted BD1, BD2, and SAB GWAS, retaining only cohorts with at least 30 subtype cases and filtering SNPs for MAF > 0.02. Results were combined across cohorts using an inverse variance-weighted fixed-effects meta-analysis[69]. We used Plink 'clumping'[70,71] to identify an LD-pruned set of discovery GWAS meta-analysis BD-associated variants ($P < 0.0001$, and distance > 500 kilobases (kb) or LD $r^2 < 0.1$, n variants = 822) for analysis in the follow-up cohorts. Conditional analyses were conducted within each GWAS cohort and meta-analyzed as above.

Follow-up cohort analysis. In each follow-up cohort we performed BD association analysis of the 822 selected GWAS variants (when available), including genetic ancestry covariates, following quality control and analysis methods of the individual study contributors. We performed inverse variance-weighted fixed-effects meta-analyses of the association results from the follow-up cohorts, and of the discovery GWAS and follow-up analyses.

PRS analyses. We tested PRS for our primary GWAS on each GWAS cohort as a target set, using a GWAS where the target cohort was left out of the meta-analysis (Supplementary Table 2). To test genetic overlaps with other psychiatric diseases, we calculated PRS for DEPR and SCZ in our GWAS cohort BD cases[72]. In pairwise case subtype or psychosis analyses (Fig. 2 and Supplementary Table 13), we regressed outcome on the PRS adjusting for ancestry principal components and a cohort indicator using logistic regression, and visualized covariate-adjusted PRS in BD1 and BD2 subtypes (Fig. 2). Outcome sample sizes were BD1 n = 8,044, BD2 n = 3,365, SAB n = 977; BD1 cases with and without psychosis n = 2,175 and n = 798,respectively, BD2 cases with and without psychosis n = 146 and n = 660, respectively.

LD score regression. LD score regression[25,26] was used to conduct SNP heritability analyses from GWAS summary statistics. LD score regression bivariate genetic correlations attributable to genome-wide common variants were estimated between the full BD GWAS, BD subtype GWASs and other traits and disorders in LD Hub[26]. We also used LD score regression to partition heritability by genomic features[45].

Relation of BD GWAS findings to tissue and cellular gene expression. We used partitioned LD score[46,73] and DEPICT[46] regression to evaluate which somatic tissues and brain tissues were enriched in the BD GWAS. We used SMR[47,49] to identify SNPs with strong evidence of causality of brain or blood gene expression or methylation in BD risk (Supplementary Table 16), with a test for heterogeneity to exclude regions with LD between distinct causal SNPs ($P_{HET} < 0.01$).

Gene-wise and pathway analysis. Guided by rigorous method comparisons conducted by PGC members[50,74], P values quantifying the degree of association of genes and gene sets with BD were generated using MAGMA (v.1.06)[50]. We used ENSEMBL gene coordinates for 18,172 genes giving a Bonferroni-corrected P value threshold of 2.8×10^{-6}. Joint multi-SNP LD-adjusted gene-level P values were calculated using SNPs 35 kb upstream to 10 kb downstream, adjusting for LD using 1000 Genomes Project (Phase 3 v5a, MAF ≥ 0.01, European ancestry subjects)[75]. Gene sets were compiled from multiple sources. Competitive gene-set tests were conducted correcting for gene size, variant density and LD within and between genes. The pathway map (Supplementary Fig. 5) was constructed using the kernel generative topographic mapping algorithm (k-GTM) as described in ref. [76].

Genome build. All genomic coordinates are given in NCBI Build 37/UCSC hg19 (http://genome.ucsc.edu/cgi-bin/hgGateway?db=hg19).

Accession codes. Accessioned data were part of the following datasets analyzed in this study. Fat2: phs000167.v1.p1 or PGC bundle phs001254.v1.p1 (MGS nonGAIN controls). Gain: dbGAP phs000017.v3.p1 (GAIN Bip cases/controls), phs000021.v3.p2 (GAIN scz controls); also part of the PGC dbGAP bundle phs001254.v1.p1. Jjst: phs000092.v1.p1 or PGC bundle phs001254.v1.p1 (SAGE controls). St2c, NIMH RGR Bipolar Study 19 (STEP-BD; https://www.nimhgenetics.org/download-tool/BP), dbGAP phs000294.v1.p1 (MIGEN controls). Mich: NIMH RGR Bipolar Study 2 (Pritzker). Wtcc: EGAD00000000002.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The PGC's policy is to make genome-wide summary results public. Summary statistics for our meta-analysis are available through the PGC (https://www.med.unc.edu/pgc/results-and-downloads). Data are accessible with collaborative analysis proposals through the Bipolar Disorder Working Group of the PGC (https://med.unc.edu/pgc).

References

69. Ripke, S. *Ricopili: a Tool for Visualizing Regions of Interest in Select GWAS Data Sets* (Broad Institute, 2014).
70. Purcell, S. et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
71. Chang, C. C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
72. Euesden, J., Lewis, C. M. & O'Reilly, P. F. PRSice: Polygenic Risk Score software. *Bioinformatics* **31**, 1466–1468 (2015).
73. Finucane, H. et al. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621–629 (2018).
74. O'Dushlaine, C. et al. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat. Neurosci.* **18**, 199–209 (2015).
75. 1000 Genomes Project Consortium et al. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
76. Olier, I., Vellido, A. & Giraldo, J. Kernel generative topographic mapping. In *Proc. 18th European Symposium on Artificial Neural Networks* (ed. Verleysen, M.) 481–486 (ESANN, 2010).

nature research

Corresponding author(s): Eli A. Stahl, John Kelsoe

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Data were generated at many sites using standard genotype calling softwares from commercial sources (Affymetrix and Illumina).
Data analysis	Analyses were performed using the Ricopili software suite, which provides wrappers for standard genetic analysis software including plink v1.09, shapeit and impute2. All of these are publicly available. Any additional analysis code is detailed in Methods and the Supplementary Note.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Full summary statistics for the GWAS will be made available through the Psychiatric Genomics Consortium (PGC), at https://www.med.unc.edu/pgc/results-and-

downloads/downloads. Data are available for analysis through the PGC Bipolar disorder working group, via collaborative analysis proposals; see https://www.med.unc.edu/pgc/shared-methods for details.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was not predetermined, but was maximized by the inclusion of datasets in this study. Sample sizes in this study are larger than previous analyses, which revealed some significant findings and showed that additional true positives remained to be discovered.
Data exclusions	Predetermined phenotypic data exclusions, for both cases and controls, are detailed in the Supplementary Note. Genotype data exclusions were also predetermined and were performed for quality control; these included high missing call rate, high or low heterozygosity, inconsistent genotype versus clinical data sex, and ancestry outlier status based on visual inspection of genotype principal component analysis results.
Replication	Follow-up samples were tested for SNPs identified as significant with P<1e-4 in our primary GWAS. Significance was defined as P<5e-8 in the combined GWAS+follow-up samples analysis. Consistency of association signal across datasets and rates of combined analysis significance were assessed as detailed in the Supplementary Note.
Randomization	Samples/participants were allocated into experimental groups by clinical cohort (which included country of origin) and genotype data collection batches. Association analyses were performed in each dataset and meta-analyzed across datasets. Ancestry covariates derived from genotype principal components analysis were included in association tests, which were logistic regression.
Blinding	Standard quality control and analysis pipelines were run such that blinding is not relevant to this study.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Research animals
☐	☒ Human research participants

Human research participants

Policy information about studies involving human research participants

Population characteristics	Human subjects were used in the datasets that were analyzed as part of this study, as described in Methods and the Supplementary Note. Phenotypes used and covariates assessed and used in analyses are also described. All local IRBs approved of this study.

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ Magnetic resonance imaging